

A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression.

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Public Summary:

The genome is extensively transcribed into long intergenic noncoding RNAs (lincRNAs), many of which are implicated in gene silencing. Potential roles of lincRNAs in gene activation are much less understood. Development and homeostasis require coordinate regulation of neighbouring genes through a process termed locus control. Some locus control elements and enhancers transcribe lincRNAs, hinting at possible roles in long-range control. In vertebrates, 39 Hox genes, encoding homeodomain transcription factors critical for positional identity, are clustered in four chromosomal loci; the Hox genes are expressed in nested anterior-posterior and proximal-distal patterns colinear with their genomic position from 3' to 5' of the cluster. Here we identify HOTTIP, a lincRNA transcribed from the 5' tip of the HOXA locus that coordinates the activation of several 5' HOXA genes in vivo. Chromosomal looping brings HOTTIP into close proximity to its target genes. HOTTIP RNA binds the adaptor protein WDR5 directly and targets WDR5/MLL complexes across HOXA, driving histone H3 lysine 4 trimethylation and gene transcription. Induced proximity is necessary and sufficient for HOTTIP RNA activation of its target genes. Thus, by serving as key intermediates that transmit information from higher order chromosomal looping into chromatin modifications, lincRNAs may organize chromatin domains to coordinate long-range gene activation.

Scientific Abstract:

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